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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,425	01/26/2001	Xaveer Van Ostade	4644US	8053

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EXAMINER
LI, RUIXIANG

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/771,425	OSTADE ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14-16,18 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-16,18 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application

The Request filed on April 17, 2003 for Continued Examination (RCE) under 37 CFR 1.114 of Application 09/771,425 is granted. An action on the RCE follows.

Applicants' Amendment

Applicants' amendment in Paper No. 16 filed on March 18, 2003 has been entered in full. Claims 17 and 19 have been canceled. Claims 24 and 25 have been added. Claims 6, 11, 15, 16, and 18 have been amended. Claims 1-11, 14-16, 18, and 21 –25 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

Applicants have cancelled claims 17 and 19, rendering all the rejections related claims 17 and 19 moot.

The rejection of claims 1-11, 14-16, 18, and 21–25 under 35 U.S.C. 103(a) set forth in Paper No. 9 and 13 have been withdrawn.

Claim Rejections Under 35 U. S. C. § 112, 2nd paragraph

The rejection of claims 11, 15, and 18 under 35 U.S.C. 112, 2nd paragraph set forth in the record remains. The newly added claims 24, 25, and claims 16 and 17 that depend upon claim 24, are also rejected under 35 U.S.C. 112, 2nd paragraph. The claims are indefinite because the steps recited by the methods do not necessarily achieve the goal set forth in the claim preamble.

Claim 11 recite a method of screening a compound that inhibits the binding of a ligand. However, the steps set forth in the method do not necessarily screen a compound that inhibits the binding of a ligand to the receptor because inactivation of cell's reporter system can occur via either inhibition of the binding of a ligand to the receptor or inhibition of a down stream signaling pathway linked to the reporter system (for example, an antagonist).

Claims 15 and 18 recite a method of screening for ligands of an orphan receptor. However, the steps set forth in the method do not necessarily screen a ligand because a compound that activates the autocrine loop and the cell's reporter system can be an agonist of the receptor, which does not act via binding to the receptor. In contrast, a ligand must bind to its receptor. There is no requirement for the compound to bind to the receptor in the steps of the method.

Claims 24 and 25 recite a method of screening for antagonists inhibiting ligand-receptor binding. However, the steps set forth in the method do not necessarily screen an

antagonist inhibiting ligand-receptor binding because assaying the activation of the reporter system does not necessarily provide information on the inhibition of ligand-receptor binding. A compound (antagonist) can cause deactivation of the reporter system via inhibiting a down stream signaling pathway linked to the reporter system.

Claim Rejections Under 35 U. S. C. § 103 (a)

(i) Claims 1-6, 10, 11, 14-16, 18, and 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pestka et al. (WO 98/02558, January 22, 1998) in view of Trueheart et al. (*IDS*, WO 98/13513, April 2, 1998).

Pestka et al. teach numerous chimeric receptors for cellular activation comprising an extracellular domain capable of binding to a cognate molecule, and a cytokine intracellular domain capable of interacting with a Jak-Stat protein, thereby participating signal transduction, with the proviso that the cytokine interacellular domain is not naturally associated with the extracellular domain (See, e.g., Abstract). The chimeric receptors accomplish receptor dimerization or oligomerization (2nd paragraph of page 9). Pestka et al. teach expression vectors expressing the chimeric receptor proteins (3rd paragraph of page 10; page 29) and expression of such chimeric receptors in bacterial, yeast, eukaryotic cells, preferably in mammalian cells including 2fTGH cells (5th paragraph of page 10; page 39; Figures 1-19). For example, Pestka et al. teach expression of various chimeric receptors in COS-1 cells (Fig. 2); Hu-IL-10R/γR1 chimeric receptor in hamster cells; EpoR/γR1 and EpoR/γR2 (erythropoietin-interferon γ receptors) in CHO-16-9 cells (Fig. 15). In these examples, the cytoplasmic part of the

chimeric receptor is a cytoplasmic part of interferon γ receptor. In response to IL-10, the Hu-IL-10R/γR1 chimeric receptor was activated and HLA-B7 surface antigen in hamster cells was induced (Example 2). Likewise, on activation by EPO which was exogenously added to cells, the chimeric receptor formed homodimers or heterodimers and the cells expressing the chimeric receptor exhibited enahnced class I MHC antigen expression (Example 3).

Pestka et al. teach a method for identifying a specific ligand, an agonist, or an antagonist using routine screening techniques and a highly sensitive assay cell line that express a chimeric receptor (bottom of page 44 to page 47). Pestka et al. also teach various screening techniques, such as natural product libraries, combinatorial libraries using recombinant bacteriophage, and synthetic libraries. Pestka et al. further teach detection of chimeric receptor-mediated activation (or inhibition of activation) can be accomplished by evaluating changes in cell targets, such as those discussed above.

Pestka et al. fail to teach a eukaryotic cell comprising a second recombinant gene encoding a compound the expression of which creates an autocrine or anti-autocrinic loop and the use of such a cell in the screening method.

Trueheart et al. teach expression of a large number of polypeptides in a library in a cell to identify those polypeptides that agonize or antagonize receptor bioacitivity, creating an autocrine system (page 3, last paragraph; page 51). Trueheart et al. also teach

expression systems (expression vectors, promoters, etc.) used for production of polypeptides in a cDNA library (See, page 22, expression systems)

Trueheart et al. further teach a method for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate the activity of a receptor. The method enables rapid screening of large numbers of compounds to identify those that act as an agonist or antagonist (inhibitor) to the bioactivity of the receptor (See abstract). The method enables rapid screening of large numbers of polypeptides in a library expressed in the cell in order to identify those polypeptides which create an autocrine system (page 3, last paragraph). The autocrine assay is characterized by the use of a library of recombinant cells, each cell of which includes a target receptor protein whose signal transduction activity can be modulated by interaction with an extracellular signal, the transduction activity being able to generate a detectable signal, and an expressible recombinant gene encoding an exogenous test polypeptide from a polypeptide library (page 3, last paragraph). The specific examples refer to activation of the pherome pathway in yeast by heterologous receptors, however, it is stated that other cells (including eukaryotic cells) can be used as host cells (see page 2, last paragraph or page 20). Trueheart et al. also teach the use of several target receptors such as cytokine receptors (page 26), receptor tyrosine kinases (page 30), and G-protein coupled receptors (page 32). Trueheart et al. further teach use of the method for identifying ligands for an orphan receptor (page 9, 3rd paragraph).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made, as a matter of choice, instead of exogenous addition of a test compound to cells, to use a second gene encoding a compound taught by Trueheart et al. so that a compound can be expressed, an autocrine or anti-autocrine loop can be created in cells taught by Pestka et al., and such cells can be used for the screening method taught by Pestka et al. with a reasonable expectation of success. One would have been motivated to do so because endogenous expression of polypeptides in a cDNA library allows rapid screening of large numbers of polypeptides as taught and by Trueheart et al. (see, e.g., page 3, last paragraph). It would have also been obvious to one having ordinary skill in the art at the time the invention was made to apply the screening method taught by Trueheart et al. in identifying a specific ligand, an agonist, or an antagonist for the chimeric receptors taught by to Pestka et al. with a reasonable expectation of success. One would have been motivated to do so because the chimeric receptors can be readily expressed in cells and used for screening their ligands, agonists, or antagonists, as demonstrated by Pestka et al.

(ii) Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pestka et al. (WO 98/02558, January 22, 1998) in view of Trueheart et al. (*IDS*, WO 98/13513, April 2, 1998) as applied to claims 1-6, 10, 11, 14-16, 18, and 21-25 above, and further in view of Pellegrini et al. (*IDS*, *Molecular and Cellular Biology* 9:4605-4612, 1989).

The combined references of Pestka et al. and and Trueheart et al. teach screening methods of using eukaryotice cells comprising a chimeric receptor, an autocrine system and a reporter system polypeptides in a cDNA library as applied to claims 1-6, 10, 11, 14-16, 18, and 21-25 above. Neither Pestka et al. nor Trueheart et al. teach a reporter system comprising *E. coli* xanthineguanine phosphoribosyl transferase (*gpt*) under control of a 6-16 promoter.

Pellegrini et al. teach the use of *gpt* as a reporter (marker) which is placed under control of a 6-16 promoter in 2fTGH cells (Abstract; page 4605, right column, 1st paragraph; Fig. 1). Pellegrini et al. teach that the 6-16 promoter is tightly regulated by α or β interferon (page 4605, bottom of left column; page 4610, 1st paragraph of Discussion).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to construct the reporter system as taught by Pellegrini et al. and to express the chimeric receptors in 2fTGH cells with a reasonable expectation of success. One would have been motivated to do so because (i) Pestka et al. teach chimeric receptors comprising an intracellular domain of an α-interfereon receptor (See, e.g., Figure 2); and (ii) the reporter system (*gpt* gene as a reporter under control of the 6-16 promoter) is responsive to α-interfereon as taught by Pellegrini et al.

(iii) Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pestka et al. (WO 98/02558, January 22, 1998) in view of Trueheart et al. (*IDS*, WO 98/13513, April

2, 1998) as applied to claims 1-6, 10, 11, 14-16, 18, and 21-25 above, and further in view of Mizushima et al. (Nucleic Acids Research, 18:5322, 1990).

The combined references of Pestka et al. and and Trueheart et al. teach screening methods of using eukaryotice cells comprising a chimeric receptor, an autocrine system and a reporter system polypeptides in a cDNA library as applied to claims 1-6, 10, 11, 14-16, 18, and 21-25 above. Neither Pestka et al. et al. nor Trueheart et al. teach the second recombinant gene inserted after an Sra or HEF1a promoter.

Mizushima et al. teach a mammalian expression vector containing HEF1a promoter. Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to insert the second recombinant gene after the HEF1a promoter with a reasonable expectation of success. One would have been motivated to do so because the HEF1a promoter stimulates very efficiently the in vivo transcription, as taught by Mizushima et al.

Prior Art of Record

The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ruixiang Li
Examiner
June 6, 2003